PATENT COOPERATION TREATY

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF ELECTION (PCT Rule 61.2)	Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202
Date of mailing (day/month/year)	ETATS-UNIS D'AMERIQUE
09 July 2001 (09.07.01)	in its capacity as elected Office
International application No.	Applicant's or agent's file reference
PCT/EP00/09132	0099351-WSmi
International filing date (day/month/year)	Priority date (day/month/year)
18 September 2000 (18.09.00)	24 September 1999 (24.09.99)
Applicant	
DEN DAAS, Izaak et al	
221. 274 to / 1254k of 61	
1. The designated Office is hereby notified of its election made X in the demand filed with the International Preliminary 27 March 2001 in a notice effecting later election filed with the International Preliminary 2. The election X was was not made before the expiration of 19 months from the priority de Rule 32.2(b).	Examining Authority on: (27.03.01) ational Bureau on:
1	Authorized officer

Form PCT/IB/331 (July 1992)

Facsimile No.: (41-22) 740.14.35

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(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 5 April 2001 (05.04.2001)

PCT

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- C12N 15/12,
- (21) International Application Number: PCT/EP00/09132
- (22) International Filing Date:

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Lung Liver SKM Kidney Testis

(25) Filing Language:

English

(26) Publication Language:

English

- (30) Priority Data: 99118848.3 24 September 1999 (24.09.1999) E
- (71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DEN DAAS, Izaak

[DE/DE]; Schillerstr. 76, 64407 Fränkisch Crumbach (DE). DÜCKER, Klaus [DE/DE]; Ettesterstr. 5, 64291 Darmstadt (DE).

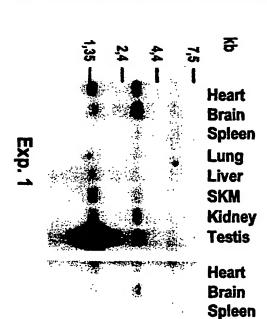
- (74) Common Representative: MERCK PATENT GMBH; 64271 Darmstadt (DE).
- (81) Designated States (national): CA, JP, US.
- (84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HUMAN PARALOGUE OF A HEAD TRAUMA INDUCED CYTOPLASMATIC CALCIUM BINDING PROTEIN



(57) Abstract: ANIC-BP-2 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing ANIC-BP-2 polypeptides and polynucleotides in diagnostic assays.

O 01/23552 A1

SEQUENCE LISTING

<110> Merck Patent GmbH

5 <120> Novelacute neuronal induced Calcium binding protein

<130> ANICBP2IDWS

<140>

10

<141>

<160> 2

15 <170> PatentIn Ver. 2.1

<210> 1

<211> 1014

<212> DNA

20 <213> Homo sapiens

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5 aaa aag aca gac aag gct tca gaa gtg tct aaa tca ctg caa gca 144 Lys Lys Thr Asp Lys Ala Ser Glu Glu Val Ser Lys Ser Leu Gln Ala

atg aaa gaa att ctg tgt ggt aca aac gag aaa gaa ccc cca aca gaa 192 0 Met Lys Glu Ile Leu Cys Gly Thr Asn Glu Lys Glu Pro Pro Thr Glu

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aca ctg ata gct gac ctg cag ctg ata gac ttt gag gga aaa aaa gat 288 Thr Leu Ile Ala Asp Leu Gln Leu Ile Asp Phe Glu Gly Lys Lys Asp

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Val Thr Gln Ile Phe Asn Asn Ile Leu Arg Arg Gln Ile Gly Thr Arg
100 105 110

55 agt cct act gtg gag tat att agt gct cat cct cat atc ctg ttt atg 384 Ser Pro Thr Val Glu Tyr Ile Ser Ala His Pro His Ile Leu Phe Met 115 120 125

ctc ctc aaa gga tat gaa gcc cca cag att gcc tta cgt tgt ggg att 432 60 Leu Leu Lys Gly Tyr Glu Ala Pro Gln Ile Ala Leu Arg Cys Gly Ile 130 135 140 HODEBYN DWENDR

5				gaa Glu													480
J				caa Gln													528
10				gct Ala 180													576
15				gtg Val													624
20				gac Asp													672
25				tct Ser													720
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30				aac Asn 260													816
35	gcc Ala	ttt Phe	cat His 275	gtt Val	ttt Phe	aag Lys	gtg Val	ttt Phe 280	gtg Val	gcc Ala	agt Ser	cct Pro	cac His 285	aaa Lys	aca Thr	cag Gln	864
40				gag Glu													912
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50	cct Pro	tga															1014
55	<21 <21	0> 2 1> 3 2> P 3> H	RT	sapi	ens												
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			35	Asp				40				-	45			
5	Met	Lys 50	Glu	Ile	Leu	Cys	Gly 55	Thr	Asn	Glu	Lys	Glu 60	Pro	Pro	Thr	Glu
	Ala 65	Val	Ala	Gln	Leu	Ala 70	Gln	Glu	Leu	Tyr	Ser 75	Ser	Gly	Leu	Leu	Val 80
10	Thr	Leu	Ile	Ala	Asp 85	Leu	Gln	Leu	Ile	Asp 90	Phe	Glu	Gly	Lys	Lys 95	Asp
				Ile 100					105					110		
	Ser	Pro	Thr 115	Val	Glu	Tyr	Ile	Ser 120	Ala	His	Pro	His	Ile 125	Leu	Phe	Met
15		130		Gly			135					140	_	_	_	
	145			Glu		150					155					160
20				Gln	165					170					175	
				Ala 180					185			-		190		
٠			195	Val				200					205	•	_	
25		210		Asp			215					220				
	225			Ser		230					235					240
30				Ile	245					250					255	
				Asn 260					265					270		
			275	Val		_		280					285	-		
35		290		Glu			295					300				
	305			Phe		310					315					320
40		Lys	Asn	Tyr	Leu 325	Ile	Lys	Gln	Ile	Arg 330	Asp	Leu	Lys	Lys	Thr 335	Ala
	Pro															

- 3 -

Pro

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference		of Transmittal of International Search Report 220) as well as, where applicable, item 5 below.							
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)							
PCT/EP 00/09132	18/09/2000	24/09/1999							
	18/09/2000	24/09/1999							
Applicant									
MERCK PATENT GMBH et al.									
This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.									
This International Search Report consists It is also accompanied by	s of a total of3 sheets. If a copy of each prior art document cited in this	s report.							
Basis of the report		-							
	international search was carried out on the balless otherwise indicated under this item.	isis of the international application in the							
the international search v Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of	the international application furnished to this							
was carried out on the basis of th	e sequence listing : onal application in written form.	nternational application, the international search							
H	ernational application in computer readable for	m.							
	this Authority in written form.								
1	o this Authority in computer readble form. bsequently furnished written sequence listing o	lace not as boyand the disclosure in the							
international application a	as filed has been furnished.	sees not go beyond the disclosure in the							
the statement that the info	ormation recorded in computer readable form	is identical to the written sequence listing has been							
2. Certain claims were fou	ind unsearchable (See Box I).								
3. Unity of invention is lac	king (see Box II).								
4. With regard to the title ,									
l <u>–</u> ''	ubmitted by the applicant.								
	shed by this Authority to read as follows:								
HUMAN PARALOGUE OF A HEAD TRAUMA INDUCED CYTOPLASMATIC CALCIUM BINDING PROTEIN									
5. With regard to the abstract,									
the text is approved as su	ubmitted by the applicant.	, (
the text has been establis	• • • • • • • • • • • • • • • • • • • •	ity as it appears in Box III. The applicant may, port, submit comments to this Authority.							
6. The figure of the drawings to be pub	lished with the abstract is Figure No.	1							
as suggested by the appl	icant.	None of the figures.							
_ X because the applicant fai	led to suggest a figure.								
because this figure better	characterizes the invention.								

International Application No EP 00/09132

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C07K14/47

C07K16/18 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, STRAND, BIOSIS, EMBASE

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х	EMBL Database, Heidelberg, FRG Emest_Hum20 accession number AA278473 03 April 1997 NCI-CGAP: "zs81h12.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE: 703943 5' similar to SW:M025_MOUSE Q06138 M025 PROTEIN; mRNA sequence" XP002133736	1,4
Y X	the whole document -& EMBL Database, Heidelberg, FRG Emest_Hum20 accession number AA279145 03 April 1997 NCI-CGAP: "zs81h12.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE: 703943 3' similar to SW:M025_MOUSE Q06138 M025 PROTEIN; mRNA sequence"	2,3,5-8 1,4
ľ	XP002133737 the whole document/	2,3,5-8

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents: A* document defining the general state of the art which is not considered to be of particular relevance E* earlier document but published on or after the international filing date C* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) O* document referring to an oral disclosure, use, exhibition or other means P* document.published prior to the international filing date but later than the priority date claimed	 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report $16/03/2001$
28 February 2001	Authorized officer
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuchs, U

2

International Application No

		1 00	/ U9132
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
Y	MIYAMOTO, H. ET AL.: "Molecular Cloning of a Novel mRNA Sequence Expressed in Cleavage Stage Mouse Embryos" MOLECULAR REPRODUCTION AND DEVELOPMENT, vol. 34, no. 1, January 1993 (1993-01), pages 1-7, XPO00892775 cited in the application clone: MO25		2,3,5-8 1,4,9-11
	the whole document		, ,
Ρ,Χ	WO 00 29580 A (INCYTE PHARMACEUTICALS, INC.) 25 May 2000 (2000-05-25) SEQ ID NOS: 1 and 2 the whole document		1-8,10
A *	DATABASE SCISEARCH 'Online! JOUNAL OF NEUROSCIENCE RESEARCH, vol. 42, no. 3, 15 October 1995 (1995-10-15) MATTSON, M.P. ET AL.: "Brain injury and tumor necrosis factors induce calbindin D-28K in astrocytes - evidence for a cytoprotective response" XP002161739 abstract		1-11

Information on patent family members

International Application No

Patent family member(s) Publication Publication Patent document cited in search report date date US 06-06-2000 WO 0029580 Α 25-05-2000 6071721 A ΑU 1724300 A 05-06-2000



PCT

REC'D 3.1 JAN 2002

....DO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applies	ent's or a	gent's file reference									
1	351-WS		FOR FURTHER ACTION		cation of Transmittal of International y Examination Report (Form PCT/IPEA/4)	16)					
Interna	tional ap	olication No.	International filing date (day/mo	nth/year)	Priority date (day/month/year)	-					
PCT/I	EP00/0	9132	18/09/2000		24/09/1999	-					
	115/12	tent Classification (IPC) or na	tional classification and IPC								
MERC	CK PAT	ENT GMBH et al.									
1. Th	nis interr nd is trar	national preliminary exami examitted to the applicant a	nation report has been prepa ccording to Article 36.	red by this Inte	ernational Preliminary Examining Aut	hority					
2. Tr	nis REP	ORT consists of a total of	8 sheets, including this cover	sheet.							
	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).										
Th	iese anr	nexes consist of a total of	sheets.								
3. Th	is repor	t contains indications relat	ing to the following items:								
	ı 🛭	Basis of the report									
	II 🗆										
	III 🗆	Non-establishment of op	inion with regard to novelty, i	nventive step	and industrial applicability						
ı	v 🗆										
	v 🛭	Reasoned statement uncitations and explanation	der Article 35(2) with regard t ns suporting such statement	o novelty, inve	ntive step or industrial applicability;						
\	vı ⊠	Certain documents cited	t								
٧	′II ⊠	Certain defects in the int	ernational application								
VI	III 🛚	Certain observations on	the international application								
Date of	submissio	on of the demand	Date of	of completion of	his report						
27/03/2	2001		29.01	2002							
	ary exam	g address of the international ining authority:	Autho	ized officer	groicoes.	MILNER					
<u> </u>	D-80	pean Patent Office 0298 Munich +49 89 2399 - 0 Tx: 523656 (Buch	et, A	Dictional Community)) in					
		+49 89 2399 - 4465		one No. ±49.89	2390 7401	THE W					

Telephone No. +49 89 2399 7401

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09132

I.	Ba	sis of the report						
1. With regard to the elements of the international application (Replacement sheets which have been furnished the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:								
	1-3	4 as originally filed						
	Cla	ims, No.:						
	1-1	1 as originally filed						
Drawings, sheets:								
	1/1	as originally filed						
	Sequence listing part of the description, pages:							
	1-3,	as originally filed						
2.	Witl lang	n regard to the language, all the elements marked above were available or furnished to this Authority in the juage in which the international application was filed, unless otherwise indicated under this item.						
	The	se elements were available or furnished to this Authority in the following language: , which is:						
		the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).						
		the language of publication of the international application (under Rule 48.3(b)).						
		the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).						
3.	With	regard to any nucleotide and/or amino acid sequence disclosed in the international application, the regard to any nucleotide and/or amino acid sequence disclosed in the international application, the regard to any or any or actional preliminary examination was carried out on the basis of the sequence listing:						
	\boxtimes	contained in the international application in written form.						
	×	filed together with the international application in computer readable form.						
		furnished subsequently to this Authority in written form.						

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in

☐ The statement that the information recorded in computer readable form is identical to the written sequence

4. The amendments have resulted in the cancellation of:

 \Box furnished subsequently to this Authority in computer readable form.

the international application as filed has been furnished.

listing has been furnished.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09132

		the description,	pages:		
		the claims,	Nos.:		
		the drawings,	sheets:		
5.		This report has been considered to go bey	establishe	ed as if (s isclosure	some of) the amendments had not been made, since they have bee as filed (Rule 70.2(c)):
		(Any replacement shi report.)	eet contai	ning such	amendments must be referred to under item 1 and annexed to this
6.	Add	litional observations, if	necessar	y:	
V.		soned statement un tions and explanatio			ith regard to novelty, inventive step or industrial applicability;
1.	Stat	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	2-3, 5, 9-11 1, 4, 6-8
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-11
	Indu	strial applicability (IA)	Yes:	Claims	1-11

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

No:

Claims

International application No. PCT/EP00/09132

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet



Reference is made to the following documents:

D1: EMBL Database

Accession number AA278473

D2: EMBL Database

Accession number AA279145

D3: Molecular Reproduction and Development

vol. 34, n° 1, 1993, pp 1-7

Re Item I

Basis of the report

This report is also established on the basis of pages 1 to 3 of the sequence listing (SEQ ID NOS: 1-2).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Novelty:

- D1 reports the sequence of a 563 bp cDNA clone (harbored by the pT7T3D-Pac vector transformed in the DH10B host cell), isolated from a human germinal center B cell library. Its similarity with the mouse MO25 calcium binding protein is mentioned.
- A sequence comparison reveals that the 563 bp fragment isolated in D1 displays 98.6% identity with the 129-690 region of SEQ ID NO: 1. Moreover, the corresponding translation product, deducible on the basis of the similarity with MO25, displays 97.3% identity with the 45-230 fragment of SEQ ID NO: 2 of the invention.
- Therefore, D1 is considered to anticipate the subject-matter of claims 1, 4 and 6-8.
- D2 reports the sequence of a 480 bp cDNA clone (harbored by the pT7T3D-Pac vector transformed in the DH10B host cell), isolated from a human germinal center B cell library. Its similarity with the mouse MO25 calcium binding protein is mentioned.

International application No. PCT/EP00/09132

- A sequence comparison reveals that the 480 bp fragment isolated in D2 contains the inverse complementary sequence of the 731-1014 region of SEQ ID NO: 1 of the invention. Moreover, the corresponding translation product, deducible on the basis of the similarity with the mouse MO25 protein, corresponds to the 243-337 fragment of SEQ ID NO: 2 of the invention.
- Therefore, D2 is considered to anticipate the subject-matter of claims 1, 4 and 6-8.
- D3 reports the sequence of a mouse gene isolated on the basis of its overexpression during early mouse development. This gene encodes a 341 aa protein (Fig. 4) which sequence displays the characteristics of calcium binding proteins (Fig. 5). It was indeed shown that a GST-MO25 fusion protein actually binds to Ca2+ (see p 6, last paragraph of the Discussion). It is intended to produce specific antibodies to gain more insight into the localization and function of said protein.
- A sequence comparison reveals that MO25 displays 80.7% identity in 337 aa overlap with SEQ ID NO: 2 of the invention.
- MO25 being considered as a "variant" of the polypeptide of the invention (see also Item VIII-1), its disclosure deprives claims 1, 4 and 6-8 of novelty.
- For all these reasons, claims 1, 4 and 6-8 do not meet the requirements of Article 33.2 PCT.

2) Inventive step:

- Claims 9 to 11 relating to fusion proteins, antibodies or methods for screening activators or inhibitors - do not contain further inventive matter which goes beyond usual skill: there are common practises for the skilled person having isolated a protein of interest (see e. g. D3).
- The contribution of the present application is considered to reside in the isolation of the full-length human gene encoding the homologue of the mouse MO25 calcium binding protein.
- Two fragments of this gene being disclosed in D1 and D2, the skilled person would have used them as probes to screen an adequate human library (e. g. genomic) with reasonable expectation of success. Therefore, the subject-matter of claims 2-3 and 5 is

International application No. PCT/EP00/09132

EXAMINATION REPORT - SEPARATE SHEET

not considered to involve an inventive step.

- For all these reasons, claims 1 to 11 do not fulfil the requirements of Article 33.3 PCT.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 00/29580	25.05.00	18.09.00	24.09.99-

Re Item VII

Certain defects in the international application

- Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

- 1) The terms "fragments" and "variants" (claims 1 and 4) are so vague and unclear that they render the scope of the invention for which protection is sought indefinite (Article 6 PCT; see also novelty objections).
- 2) The polynucleotide claimed in part (e) of claim 4 is defined by the method which allows to isolate it (product by process). This definition which is unclear and does not unambiguously define said product is not acceptable: A polynucleotide should be defined by its sequence (Article 6 PCT).

EXAMINATION REPORT - SEPARATE SHEET

3) It appears that the subject matter of claim 7 should be the subject of 2 distinct claims.